REMARKS

Claims 48 and 55 are currently pending in the application. Claims 1-47 and 49-54 have been cancelled. Applicants reserve the right to pursue these or other claims under separate prosecution.

Claims 48 and 55 are currently amended, and support for the amendments are in the specification at page 10, lines 5-7; page 33, lines 18-21; and page 52, lines 11-18. Claims 56 and 57 have been added and find support in the specification at, for example, page 10, lines 15-19. No new matter has been added by way of the claim amendments and additions.

Issues Regarding Priority

On page 3 of the Action, the Office alleges that claims directed to nucleic acids encoding an *atonal*-associated fusion protein are not entitled to the benefit of the filing date of U.S. Provisional Patent Application No. 60/137,060, filed June 1, 1999. This interpretation is in error. In fact, in the paragraph beginning on page 7, line 21, of the specification of U.S. Provisional Patent Application No. 60/137,060, Applicants teach a composition that includes a *Math1* protein or gene. The specification further proceeds to state that the *Math1* composition may include fusion proteins. Furthermore, the U.S. provisional patent application contains claims directed to *atonal*-associated fusion proteins, namely claim 60, which is directed to a *Math1* fusion protein.

Furthermore, it is noted that the specification teaches a family of bHLH factors, including *Drosophila atonal* (see specification of U.S. Provisional Patent Application No. 60/137,060 at, for example, page 2, lines 8-15, and page 13, lines 18-21). *Math1*, itself, is noted as an *atonal* homolog (see specification of U.S. Provisional Patent Application No. 60/137,060 at, for example, page 3, lines 19-20, and page 5, line 8), and the Xenopus homolog *Xath1* (see specification of U.S. Provisional Patent Application No. 60/137,060 at, for example, page 14, lines 14-17) also is described. These are all clearly "*atonal*-associated" examples, given that *atonal* itself is part of their full gene names. As stated in MPEP 2163.02, "the subject matter of the claim need not be described literally (*i.e.*, using the same terms or *in haec verba*) in order for the disclosure to satisfy the written description requirement". Given that the written description need not be literal for the term, Applicants appropriately claim priority for the pending claims back to U.S. Provisional Patent

Application No. 60/137,060, filed June 1, 1999.Regarding the issue under 37 CFR 1.78(a)(2) and (a)(5), Applicants herein amend the specification to include the appropriate claim for priority. A corrected filing receipt has been requested.

Furthermore, the Examiner asserts on page 3 of the Action that a certified copy of the application as required by 35 USC 119(b) was not filed. However, the Office Action Summary states that the copies were received from the International Bureau. Applicants request clarification of this issue from the Examiner.

Issues Regarding the Specification

The Examiner requested amendments to the specification regarding particular notations of sequence identification numbers for amino acid sequences set forth therein. The appropriate amendments are presented herein. SEQ ID NO:70 was not included in the sequence listing as filed, although the amino acid sequence is fully described in the specification. An amended Sequence Listing is filed herewith. No new matter has been added by way of the amended Sequence Listing.

Although the Examiner requested Applicants to return a copy of the attached Notice to Comply herewith, Applicants did not receive said document.

Issues under 35 U.S.C. §112, first paragraph; Written Description

Claims 48 and 55 are rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully disagree.

Claims 48 and 55 have been amended without acquiescence solely in an effort to advance prosecution of the current application. Applicants clearly provide adequate written description for the nucleic acid sequence encoding polypeptides comprising "about 80% identity to SEQ ID NO:58" (see, for example, page 10, lines 5-7) and comprising "at least about 80% identity to SEQ ID NO:70" (see, for example, page 33, line 18-21). Thus, the Examiner's contention that each component of the fusion protein is innumerable becomes moot, and Applicants respectfully request that the rejection be withdrawn.

The Examiner further contends that there is insufficient written description for nucleic acid sequences encoding fusion proteins and espouses that "what is required is a description

of the structure and function of the fusion protein and the nucleic acid sequence itself" (page 6 of the Action). Applicants refer the Examiner to the specification, which provides adequate written description of nucleic acid sequences encoding *atonal*-associated fusion proteins.

For example, the instant application at page 10, lines 12-19, states, "*atonal*-associated amino acid sequence or nucleic acid sequence...in combination with a delivery vehicle" and that "said vehicle is...any fusion molecule. (emphasis added)." Furthermore, under the section "*Atonal*-Associated Nucleic Acids" (see specification at, for example, page 46, line 19), the specification describes that "...nucleic acid segments can express...fusion proteins,..." (see sentence bridging pages 48-49). In addition, the specification states that fusion proteins can be prepared where the *atonal*-associated coding region is aligned within the same expression unit as other proteins having desired functions (see, for example, paragraph beginning on page 52, line 11), which represents a clear description of fusion nucleic acid sequences. Moreover, Applicants have provided particular desired embodiments as further descriptions of appropriate nucleic acid sequences encoding *atonal*-associated fusion proteins. On page 69, lines 1-4, the specification states: "Disclosed herein are compositions and methods for the use of the *Math1* gene, its human homolog (*Hath1*) or any of its homologs, orthologs, chimeric fusion proteins or derivatives of any suitable *atonal*-associated nucleic acid sequence or any another *atonal*-associated nucleic acid sequence. (emphasis added)" On page 86, lines 16-17, the specification teaches: "*Math1D* fragment was expressed as a His tag fusion protein" (emphasis added), which entails providing a nucleic acid fusion molecule. Again, on page 107, line 18, through page 108, line 1, Applicants teach the following:

> ***DNA sequences to be expressed as proteins often appear as fusion with unrelated sequences*** that encode polyhistidine tags, or HA, FLAG, myc and other epitope tags for immunochemical purification and detection, or phosphorylation sites, or protease recognition sites, or additional protein domains such as glutathione S-transferase (GST), maltose binding protein (MBP) (New England Biolabs), and so forth that facilitate purification. (emphasis added)

Also on page 108, lines 17-20, Applicants provide the following exemplary embodiment:

> In an embodiment of the present invention there are constructs containing the Tat or Tat-HA nucleic acid sequence operatively

> linked to a *Math1* nucleic acid sequence. In another embodiment these constructs include a *Hath1* or any *atonal*-associated nucleic acid sequence.

Therefore, Applicants do, in fact, teach *atonal* nucleic acid molecules encoding fusion proteins, and subject matter of the pending claims is more than sufficiently described in the instant application so as to meet the written description requirement of Section 112, first paragraph.

The Examiner further alleges that Applicants did not provide ample written description for a "therapeutically effective amount" of an *atonal* fusion protein, pursuant to claim 55. Not in acquiescence of the rejection and solely in an effort to advance prosecution of the patent application, claim 55 has been amended to remove the language cited by the Office from the claim. Thus, the rejection is moot.

The Examiner also alleges that the specification does not teach how to target cells with the compositions, and presumes that a therapeutic effect may not be desired in every cell. However, on page 107, lines 9-11, Applicants state: "*Math1* expression using recombinant constructs can be used to target the delivery of *Math1* to cells in need thereof. Different promoter-vector combinations can be chosen by a person skilled in these arts to drive *Math1* expression in different cell types." Therefore, a skilled artisan would recognize that targeting of *atonal*-associated compositions to particular cell types was described in the application, and Applicants therefore did have possession of the invention.

Regarding each aspect of the Examiner's rejections under the written description standards for §112, first paragraph addressed above, Applicants note that to satisfy the written description requirement the specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). The specification provides sufficient written description for the aspects of the invention identified by the Office, and a skilled artisan would conclude that Applicants had possession of the presently claimed invention upon filing. Furthermore, compliance with the written description requirement is essentially a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed. *Enzo Biochem*, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002). Given that the level of skill is high in molecular biology, a skilled artisan would recognize the inventor's

possession of the presently claimed invention. *Ex parte Forman*, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). For example, the specification refers to promoter-vector embodiments for targeting particular cells, which, give the high skill in the art, is sufficient for the ordinarily skilled artisan to recognize that Applicants had possession of the claimed invention upon filing. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. *Vas-Cath*, 935 F.2d at 11563, 19 U.S.P.Q.2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 U.S.P.Q. 391, 395 (C.C.P.A. 1972).

In view of the above, Applicants respectfully request withdrawal of the rejection under Section 112, first paragraph, for alleged lack of written description.

Issues under 35 U.S.C. §112, first paragraph; Enablement

Furthermore, claims 48 and 55 are rejected under 35 USC §112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants respectfully disagree.

Solely in an effort to advance prosecution of the instant application, Applicants amend the claims herein to refer to *atonal*-associated nucleic acid sequences encoding amino acid sequences comprising about 80% identity to SEQ ID NO:58 and comprising at least about 80% identity to SEQ ID NO:70. The claims are enabled by the instant specification for the reasons set forth below.

The Office reiterates the same features of the claims which formed the basis of the written description rejection as also lacking enablement by the specification. Applicants refer the Examiner to those citations noted above.

The Examiner alleges that claim 55 is not enabled due to the recitation of "therapeutically effective amount of *atonal*-associated nucleic acid sequence". While Applicants do not agree with the Office's contentions set forth in the Office Action, claim 55 has been amended to remove the language cited by the Office, thereby obviating the rejection.

The Office also contends that the claims are not enabled with respect to targeting of an *atonal* composition. However, Applicants do, in fact, teach targeting of the compositions of the invention, such as, for example, by particular promoter/vector embodiments (see, for example, page 107, lines 9-11). The generation of gene delivery constructs suitable for targeting expression of *atonal*-associated fusion proteins requires only routine molecular biology methods. Disclosure of well-known techniques or scientific principles to those of skill in the art is not required. *In re Buchner*, 929 F.2d 660, 661, 18 U.S.P.Q.2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBC v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984).

The claims are further rejected for the alleged failure of the specification to teach how to obtain a therapeutic effect *in vivo* using a nucleic acid encoding an *atonal* protein. Applicants note that the pending claims do not require any therapeutic effect to be achieved upon administering the claimed nucleic acid sequence or composition to a subject. Second, the instant specification provides ample guidance with respect to nucleic acid sequences, gene delivery vector formulations, gene delivery methods, techniques for monitoring effective gene transfer to cells, dosage and scheduling, which enables the ordinarily skilled artisan to make and use the invention as claimed using only routine experimentation. In addition, the specification teaches methods of delivering, for example, suicide genes to a subject to achieve a biological response, which provides further guidance with respect to delivering a nucleic acid sequence to a cell in a subject.

In view of the above, one of ordinary skill in the art, using the instant specification as guide, could make and use the invention at the time of filing using only routine experimentation. The Office has cited Miller, Deonarain, and Verma as allegedly supporting the unpredictability in the art of gene transfer in vivo, where certain results may be associated with a degree of unpredictability. However, M.P.E.P. § 2164.03 supports Applicants' position on enablement rather than that advanced in the Action. M.P.E.P. § 2164.03 further provides:

It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the

enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result.

Id. (quoting *In re Dreshfield*, 45 U.S.P.Q. 36 (C.C.P.A. 1940)). Furthermore, even in unpredictable arts a disclosure of every operable species is not required. (M.P.E.P. § 2164.03)

It is well settled patent law that the first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). This objective enablement may be provided through broad terminology or illustrative examples. *Id.* Thus, Applicants assert that the instant specification meets the requirement for enablement under 35 U.S.C. §112, first paragraph.

In contrast to the assessment in the Action, the present disclosure completely complies with the requirements of M.P.E.P. § 2164.03 and *In re Dreshfield* by providing both (a) a disclosure regarding a number of species of *atonal*-associated nucleic acid sequences (see, for example, page 28, line 12, through page 29, line 13; and page 46, line 19, through page 53, line 6), rather than a single species; and (b) providing a detailed description of vectors and their characteristics (see, for example, page 39, line 14, through page 44, line 6). To interchange particular elements for different vectors is absolutely rudimentary in the art. In addition, the specification provides ample guidance with respect to gene delivery to allow the ordinarily skilled artisan to deliver the claimed nucleic acid sequence to a cell (see, for example, page 55, line 13, through page 58, .ine 20).

For the reasons set forth above, the pending claims are enabled by the instant specification, and the rejection under Section 112, first paragraph, should be withdrawn.

Issues under 35 U.S.C. §112, second paragraph

Claims 48 and 55 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully disagree, but amend the claims to refer to an *atonal*-associated sequence of about 80% identity to SEQ ID NO:58 and at least about 80% identity to SEQ ID NO:70. The amendments are made solely to further

the prosecution of this case and not in acquiescence of the rejection. Applicants respectfully request that the rejection be withdrawn.

In particular, the Office objects to the phrase "desired amino acid sequence" as allegedly being indefinite. Likewise, the Office contends that the phrase "therapeutically effective amount of *atonal*-associated nucleic acid sequence" is unclear. Although Applicants respectfully disagree, the claims have been amended to cancel the language cited by the Office. The rejection for alleged indefiniteness should be withdrawn.

Issues under 35 U.S.C. §102(a) and 35 U.S.C. §102(b)

Claims 48 and 55 are rejected under 35 USC §102(a) as allegedly being anticipated by Schwarze et al. (1999). As amended herein, Schwarze does not teach that the *atonal*-associated sequence has about 80% identity to SEQ ID NO:58 and comprises at least about 80% identity to SEQ ID NO:70, as required by the pending claims. Therefore, Applicants respectfully request that the rejection be removed.

Claims 48 and 55 are rejected under 35 USC §102(b) as allegedly being anticipated by Schwab et al. (1998). As amended herein, Schwab does not teach that the *atonal*-associated sequence has about 80% identity to SEQ ID NO:58 and comprises at least about 80% identity to SEQ ID NO:70, as required by the pending claims. Thus, Applicants respectfully request that the rejection be removed.

Issues under 35 U.S.C. §103(a)

Claims 48 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Brown in view of Schwarze. Applicants respectfully disagree.

Claims 48 and 55 are directed to compositions having an *atonal*-associated sequence of about 80% identity to SEQ ID NO:58 and comprising at least about 80% identity to SEQ ID NO:70. These features are not taught or suggested by Brown, Schwarze, or the combination thereof, nor is there a motivation to preapre such compositions based on the disclosures of Brown and/or Schwarze. Therefore, Applicants respectfully request withdrawal of this rejection.

Claims 48 and 55 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Akazawa in view of Schwarze. Applicants respectfully disagree.

Claims 48 and 55 are directed to compositions having an *atonal*-associated sequence of about 80% identity to SEQ ID NO:58 and comprising at least about 80% identity to SEQ ID NO:70. These features are not taught or suggested by Azakawa, Schwarze, or the combination thereof, nor is there a motivation to prepare such compositions based on the disclosures of Azakawa and/or Schwarze. Therefore, Applicants respectfully request removal of this rejection.

Double Patenting

Claims 48 and 55 are provisionally rejected under the judicially created doctrine of double patenting over claims 112 and 117 of co-pending Application No. 09/585,645. Applicants reserve the right to address this issue upon issuance of Application No. 09/585,645.

Conclusion

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

An Amended Sequence listing is filed herewith.

Applicant believes no fee is due with this response. However, if a fee is due, please charge our Deposit Account No. 06-2375, under Order No. HO-P01899US3 from which the undersigned is authorized to draw.

Dated: July 1, 2004

Respectfully submitted,

By _____

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